matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. The Office Action acknowledges support for the recitation of "one or more receptor" as in claim 39, but alleges that the specification does not provide adequate support for the terms "two or more receptors" or "five or more receptors" as recited in claims 10-18, 40, 41 and 43.

Applicants respectfully disagree with the assertion in the Office Action that the specification as filed does not provide sufficient written description for the terms "two or more receptors" or "five or more receptors." The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the filing date. In re Kaslow, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed. Cir. 1983); Eiselstein v. Frank, 52 F.3d 1035, 34 U.S.P.Q.2d 1467 (Fed. Cir. 1995).

The specification need not provide literal support for the claim language but, rather, convey to one skilled in the art that Applicant was in possession of the claimed invention at the time the application was filed. In re Kaslow, *supra*.

> The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific

> subject matter later claimed by him; how the specification accomplishes this is not material.... It is not necessary that the application describe the claim limitations exactly..., but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.

In re Wertheim, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976) (citations omitted). In addition, the teachings in the entire specification must be considered.

> When the scope of a claim has been changed by amendment in such a way as to justify an assertion that it is directed to a *different invention* than was the original claim, it is proper to inquire whether the newly claimed subject matter was *described* in the patent application when filed as the invention of the applicant.... In deciding the issue, the specification as a whole must be considered.

In re Wright 866 F.2d 422, 424-425, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1988)(emphasis in original).

Furthermore, in In re Edwards, the C.C.P.A. articulated the function of the written description requirement, stating:

> [The f]unction of [the] description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; to comply with the description requirement, it is not necessary that the application describe the claimed invention in *ipsis*

> *verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him.

In re Edwards, 568 F.2d at 1351-52, 196 U.S.P.Q. at 467 (citations omitted).

Applicants respectfully submit that, based on the teachings in the specification, and consistent with the case law described above, one skilled in the art would have understood that Applicant was in possession of the claimed invention at the time the application was filed. In particular, one skilled in the art would have understood that Applicants were in possession of the claimed methods of determining binding of a ligand to a receptor by contacting a collective ligand variant population with a population of five or more receptors (claims 10-18, 40, and 43) or two or more receptors (claim 41) and detecting binding of a receptor from the population to a ligand from the collective ligand variant population.

In particular, the specification at page 12, lines 25-29, indicates in part that "a population of receptors can be screened with a ligand variant population" (emphasis added). In addition, the specification at page 9, lines 26-28 states "[A]s used herein, the term 'population' is intended to refer to a group of two or more different molecules." Furthermore, the specification at page 9, line 32, to page 10, line 1, states "In some embodiments, populations are between about 5 and 10

different species as well as up to hundreds or thousands of different species."

Therefore, the specification provides sufficient description for the claimed methods of determining binding of a ligand to a receptor by contacting a collective ligand variant population with a population of five or more receptors (claims 10-18, 40, and 43) or two or more receptors (claim 41) and detecting binding of a receptor from the population to a ligand from the collective ligand variant population. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Claims 10-18, 39-41, and 43 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. The Office Action acknowledges that terms such as "collective ligand variant population," "binding activity," and "optimal binding activity" are defined in the specification, but alleges that they are defined very broadly. In particular, the Office Action alleges that the term "collective ligand variant population" could encompass a virtually unlimited number of compounds because the claims give no structure for the ligand itself and no structural information as to the specific variant. Additionally, the Office Action alleges that techniques for tagging (claims 17 and 39) and

recombinantly producing ligands in melanophore cells (claims 15 and 16) are not adequately described.

Applicants maintain that the specification provides sufficient written description for the subject matter of claims 10-18, 39-41, and 43. Specifically, regarding the allegation that the "collective ligand variant population" could encompass a virtually unlimited number of compounds because the claims give no structure for the ligand itself and no structural information as to the specific variant, Applicants respectfully point out that it is not the genus of ligands or ligand variants that is being claimed, but rather methods for determining the binding of a ligand to a receptor. The claimed methods can be practiced with ligands having a variety of structures. For example, the specification teaches at page 8, lines 11-13, that "a ligand can be essentially any type of molecule such as polypeptide, nucleic acid, carbohydrate, lipid, or any organic derived compound."

While the ligand can have various structures, the "collective ligand variant population" is a group of ligands having structural and functional features based on a particular parent ligand. For example, the specification at page 8, lines 26-28, defines the term "variant" when used in reference to a ligand as a molecule that shares a similar structure and function. In addition, the specification teaches that the characteristics that define the function can be determined by a parent ligand, and that variants can possess, for example, substantially the same or similar binding function as the parent molecule (page 8, lines 29-32). The specification goes on to

teach different modifications of a parent molecule that can result in variants such as, for example, mutation of an amino acid residue, addition of a chemical moiety, or binding of a regulatory molecule (page 9, lines 3-25). Thus, the specification provides sufficient written description regarding ligands and ligand variants as used in the claimed methods.

The Office Action further alleges that the specification does not describe an example of a collective ligand variant population and that an example is required because the art is unpredictable. Applicants maintain that a working example is not required and that the art is not unpredictable. Applicants contend that one skilled in the art would be able to extrapolate working Example V to the instant claims given the teachings in the specification and what was known in the art. Applicants submit that a person of ordinary skill in the art would understand that the collective receptor variant population disclosed in Example V also can serve to exemplify a collective ligand variant population. The specification clearly teaches that "a molecule that is a ligand can also be a receptor and, conversely, a molecule that is a receptor can also be a ligand since ligands and receptors are defined as binding partners" (page 8, lines 16-19). It would also be known to one skilled in the art that when describing binding partners such as, for example, an antibody and antigen, one could just as easily categorize the antibody as the receptor or as the ligand. Therefore, as taught in the specification, a molecule that is a receptor can also be a ligand.

Specifically regarding Example V, a BR96 antibody is designated as a parent receptor and used as the basis for generating a collective receptor variant population. A population of anti-idiotypic antibodies are designated as ligands in this example. Given the teachings in the specification cited above and what was known in the art at the time of filing of the application, one skilled in the art would understand that the terms receptor and ligand are interchangeable in this example and, thus, the collective receptor variant population of BR96 antibody variants could just as easily be designated as a collective ligand variant population. Therefore, in addition to teaching the characteristics of a collective ligand variant population, the specification also provides an example of a population of molecules that can be a collective ligand variant population.

The Office Action also alleges that claims 15 and 16 require specific techniques for producing ligands which are not adequately described in the disclosure. In addition, the Office Action alleges that claim 17 and claim 39 require tagging which is not adequately described in the disclosure. Further, the Office Action alleges that there are no examples of these techniques.

Applicants maintain that the specification provides sufficient description to teach one skilled in the art how to recombinantly express a ligand variant population in cells (claim 15) and specifically in melanophore cells (claim 16). Using the description and guidance in the specification, Applicants contend

that it would have been clear to one of skill in the art how to produce ligands by recombinant expression in cells. The specification teaches in Example I specific procedures for deriving melanophore cells (page 37, line 15, to page 38, line 5) and transfecting DNA constructs into melanophore cells (page 39, lines 1-10). Although Example I exemplifys expression of a receptor in melanophore cells, one skilled in the art would clearly understand that a ligand could be expressed in melanophore cells using the same procedure. As corroboration that one skilled in the art would have known how to express constructs other than GPCR constructs in melanophores, Applicants submitted U.S. Patent No. 5,462,856 in the last Response (Exhibit A in the last Response). On page 13, lines 45-48, the patent describes an example using electroporation of a lacZ plasmid into melanophore cells. In addition, on page 14, lines 55-58, the patent describes that exogenous G proteins can be expressed in melanophores via the type of recombinant DNA technology used to express GPCRs in melanophores. Therefore, one skilled in the art would understand that in addition to recombinantly producing receptors in melanophore cells, other non-receptor polypeptides could be produced in melanophore cells using the same techniques.

In regard to tagging ligands, the specification teaches methods of tagging variants at page 28, line 28, to page 30, line 24. For example, the specification teaches that a large number of tags can be generated with a limited number of different peptides and antibodies specific for those peptides (page 29, lines 30-32). In addition, the specification gives an

example of the use of 32 different peptides to generate 4096 different tags (page 30, lines 1-4). Furthermore, the specification teaches methods for detecting the tag, for example, using antibodies specific for the peptides in FACS analysis (page 30, lines 8-20). Moreover, the specification provides an example, Example I, where a variant population is tagged by co-expression of a peptide tag on the parental expression vector (page 38, lines 18-33). Again, although Example I exemplifies tagging of a receptor, one skilled in the art would clearly understand that a ligand could be tagged using the same procedure.

Applicants respectfully submit that the specification provides sufficient description and guidance to convey to one skilled in the art that Applicants were in possession of the claimed invention at the time the application was filed. Therefore, Applicants respectfully request that these grounds of rejection be withdrawn.

Claims 10-18, 39-41, and 43 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Office Action alleges that no limitations on the specific structure of the ligand or receptor are given and, as such, they could read on a wide variety of structures. In addition, the Office Action alleges that no working examples are given and that the state of the art is unpredictable. Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods.

Regarding the alleged breadth of the claims in regard to the structure of the collective ligand variant population, as described earlier, the claims are directed to methods and not to ligand or ligand variant compositions of matter. The specification teaches that a ligand can have several different types of structures and that the collective ligand variant population is based on the structural and functional features of a particular parent ligand. Furthermore, the specification teaches in detail several methods for creating variants including codon-based mutagenesis (page 20, line 18, to page 23, line 6, and Example V, page 49, line 10, to page 50, line 28). Based on the teachings in the specification regarding ligands and receptors, and as understood by one skilled in the art, these methods for creating variants are equally applicable to a ligand variant population or a receptor variant population.

Regarding the alleged unpredictability in the art, Applicants respectfully submit that the specification provides sufficient description and guidance to enable the invention as claimed. The Office Action acknowledges that ligand/receptor binding pairs were well-known in the art at the time of the invention, however the Office Action maintains that only limited numbers of such pairs were known. Applicants submit that a number of ligand/receptor binding pairs were known in the art at the time of filing of the application, thus contributing to predictability in the art. In the last Response, Applicants provided three review articles showing that not only were a number of ligand/receptor binding pairs known in the art at the time of filing of the application, but several distinct families

of ligand/receptor pairs were known in the art. Applicants provided review articles describing several chemokine receptors, which are G-protein coupled receptors, and their corresponding ligands, several TNF receptor and ligand pairs, and several receptor tyrosine kinases and corresponding ligands (Exhibits B-D in the last Response). Thus, a number of ligand/receptor binding pairs with diverse structures were known in the art at the time of filing of the application, which contribute to predictability in the art with regard to the ligand/receptor binding partners.

The Office Action further alleges that tagging processes were unpredictable and highly dependent on compound structure and that the same is true for recombinant expression of the ligand variant population in cells because no structure of the collective ligand variant population is provided. The legal question of enablement involves an assessment of whether a patent disclosure would have enabled one of ordinary skill in the art at the time the application was filed to make and use the claimed invention without undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Applicants respectfully submit that, given the guidance provided by the specification, only standard and well-known techniques not requiring undue experimentation, would have been required to practice the invention methods.

In *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 47 U.S.P.Q.2d 1705 (Fed. Cir. 1998), the Federal Circuit clearly stated that routine experimentation does not constitute undue experimentation:

> The test [for undue experimentation] is not merely quantitative, since **a considerable amount of experimentation is permissible**, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Id. (Emphasis added) (citing *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d at 1564, 37 U.S.P.Q.2d at 1623); see also *In re Wands*, 858 F.2d at 736-40, 8 U.S.P.Q.2d at 1403-07.

Regarding unpredictability in the use of melanophore cells and adding tags to ligands, Applicants submit that the specification teaches routine methods of using melanophore cells to express variants (page 24, line 11 to page 25, line 32; Example I, pages 37-40) and routine methods for tagging with an identifiable tag (page 28, line 18 to page 30, line 24; and Example I, page 38, lines 18-33). As described further above, Applicants submit that one skilled in the art would know how to express a ligand in melanophore cells using the teachings in the specification. Therefore, Applicants submit that undue experimentation would not be required to express a ligand or a receptor in a melanophore cell.

Regarding the alleged unpredictability of adding tags to ligands, the Office Action cites an article by Janda (Proc. Natl. Acad. Sci. USA 91:10779-10785 (1994)) as describing the unpredictability of tagging methods. However, Applicants maintain that the article by Janda cites several references that

have successfully used different tagging methods. These methods include diverse tagging strategies such as phage display, a "peptides on plasmids" method by Affymax, a peptide coded library method by Chiron Corporation, electrophoric tagging, and encoded combinatorial libraries. Thus, Janda supports the teachings in the specification that one skilled in the art could expect to successfully tag a ligand variant population without undue experimentation.

The Office Action again alleges that no working examples of the claimed methods are provided. As discussed above, a working example is not required; however, a working example in the specification (Example V) describing receptor variants is applicable to ligand variants. Furthermore, the specification clearly states on page 31, lines 5-8, that "methods and procedures described above for determining binding of a receptor to one or more ligands can similarly be applied to determine the binding of a ligand to one or more receptors."

Applicants respectfully submit that the specification provides sufficient description and guidance to enable the claimed methods. Accordingly, Applicants respectfully request that these grounds of rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 10, 17, 39 and 40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting that the ligand variants are tagged. The Examiner alleges that

it is unclear as to Applicants intent since the structure of the ligand variant is not set forth in the claims. In addition, the Office Action alleges that it is unclear how polypeptide ligands are to be tagged with "peptide tags." As described further above, the explicit recitation of the structure of the ligand or ligand variant is not required in claims directed to screening methods. As for how a polypeptide could be tagged by a peptide, Applicants submit that one skilled in the art would understand that polypeptides are often expressed as chimeric proteins containing a tag such as an epitope tag. In addition, the specification teaches that "peptides that are expressed on the surface of cells and that are recognized by specific antibodies can be used as tags to identify a co-expressed receptor variant" (see page 28, lines 30-33). Furthermore, the specification teaches that each tag can be composed of specific combinations of peptides that are recognized by distinct antibodies which are used to identify the receptor variant correlated with that tag (see page 38, lines 29-33).

Claim 40 also stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting the term "organic-derived compound ligands." The Office Action alleges that "organic-derived" is a relative term which renders the claim indefinite. Applicants submit that the term "organic-derived" is a term of art. As understood by one skilled in the art, organic means relating to, or belonging to the class of chemical compounds that are formed from carbon. Therefore, the term "organic-derived compound ligands" is clear and definite.

Applicants respectfully submit that the claims are clear and definite with regard to the recitation that ligand variants are tagged and the term "organic-derived compound ligands." Accordingly, Applicants respectfully request that these grounds of rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Claim 41 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Combs et al. (J. Am. Chem. Soc. 118:287-288 (1996)). The Examiner alleges that Combs et al. discloses a method for using a library of ligands that direct non-peptide binding elements into the specificity pocket of an SH3 protein. In addition, the Office Action alleges that a particular ligand (ligand 1A) that bound to the protein kinase Src (a receptor) was also measured against the SH3 domain in the p85 component of PI3K (a second receptor) although it showed selectivity for Src SH3.

Applicants respectfully submit that claim 41 is novel over the Combs et al. reference. Applicants submit that Combs et al. reference does not teach contacting a collective ligand variant population with a population of two or more receptors, but rather describes ligands that were contacted with one "receptor" (SH3 domain from Src) and *subsequently* one ligand (ligand 1A) was contacted with another "receptor" (SH3 domain from the p85 component of PI3K) (see, for example, Combs et al., page 288, 2nd paragraph, 1st sentence).

Thus, the Combs et al. reference does not teach the method of the claimed invention and, therefore, it cannot anticipate the claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 10-14, 17, 18, 40 and 43 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Combs et al. (JACS, 118:287-288 (1996)). The Office Action alleges that the Combs et al. reference teaches testing a library against two receptors and that testing the library against further receptors would be obvious to one of ordinary skill. As described above, Applicants submit that the Combs et al. reference does not teach or suggest the contacting of a collective ligand variant population with a population of two or more receptors, but rather in the reference by Combs et al. ligands were contacted with one "receptor" and *subsequently* one ligand was contacted with another "receptor." Thus the publication by Combs et al. cannot render the claimed invention obvious. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The

Examiner is invited to call the undersigned agent or Cathryn Campbell with any questions related to this application.

Respectfully submitted,

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Date

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